

## PCT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>10277/7004W0</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/06874</b>	International filing date (day/month/year) <b>30/03/1999</b>	(Earliest) Priority Date (day/month/year) <b>17/04/1998</b>
Applicant <b>UNIVERSITY OF VERMONT</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1  
☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

I. International application No.

PCT/US 99/06874

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 50, 51, 57, 58, 84-137  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 1-3,5-9,13-16,18-20,23-26,29-34,38-39,42-49,53-56,139-142 (partially) 4,10-12,17,21,22,27,28,35-37,40,52,138 (completely) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

## Continuation of Box I.2

Claims Nos.: 50,51,57,58,84-137

A plurality of claims relate to methods/products defined by reference to a number of desirable characteristics or properties, namely

- 1) inducing agent effective to induce expression of MHC class II HLA-DR, HLA DP/DQ, Fas on the surface of mammalian cell
- 2) inducing agent effective to induce expression of B7 on the surface of the nerve cell
- 3) inducing agent effective to induce expression of CD28 in the surface of a neural activating cell
- 4) metabolic modifying/inhibiting agent, effective to increase/decrease the mitochondrial membrane potential
- 5) apoptotic chemotherapeutic agent
- 6) induce expression of a receptor for nerve growth factor
- 7) neural activating cell which induce neuronal differentiation in implanted B7 expressing neuron.

The claims cover all products/methods having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/methods comprising

- 1) administering an MHC class II HLA-DR or HLA-DP/DQ or Fas or B7 ligand, to selectively engage said molecules and decrease/increase mitochondrial membrane potential in the cell
- 2) method to induce the expression of immune recognition molecules (wherein by immune recognition molecules is meant MHC class II and B7) with a metabolic inhibition agent (fatty acid) to decrease the mitochondrial membrane potential and induce expression of said immune recognition molecules on the cell surface
- 3) adriamycin, gamma interferon, and staurosporin as inducing agent
- 4) sodium acetate as metabolic modifying agent (example 12)
- 5) method to kill cells contacting said cells with a UCP anti-sense nucleic acid.

The claims related to said above mentioned products/methods namely: 1,2,5,6,8,14,15,17,19,20,22,23,24,31,39-43,49,53,55,56,140, have been searched completely. All other claims, if not mentioned as not searched

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

claims, have been searched partially and in the light of the above mentioned searched subjects.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

Inter al Application No

PCT/US 99/06874

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K39/395 A61K38/21 A61K31/70 A61K38/17 A61K31/20  
 A61K31/55 A61K31/505 A61K35/00 A61K38/00 G01N33/574  
 C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE MEDLINE 'Online!            US NATIONAL LIBRARY OF MEDICINE (NLM),            BETHESDA, MD, US            STREET D ET AL: "Interferon-gamma enhances            susceptibility of cervical cancer cells to            lysis by tumor-specific cytotoxic T            cells."            retrieved from STN            Database accession no. 97302905            XP002122832            abstract            &amp; GYNECOLOGIC ONCOLOGY, (1997 MAY) 65 (2)            265-72. ,</p> <p style="text-align: center;">--- -/--</p>	<p>18,19,            24,79,            80,82</p>



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
 "&" document member of the same patent family

Date of the actual completion of the international search

18 November 1999

Date of mailing of the international search report

03/12/1999

Name and mailing address of the ISA

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Authorized officer

Covone, M

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/06874

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCAFFIDI C ET AL: "Two CD95 ( APO - 1 / Fas ) signaling pathways." EMBO JOURNAL, (1998 MAR 16) 17 (6) 1675-87. , XP002122827 abstract page 1676, right-hand column, paragraph 3 -page 1677, right-hand column, paragraph 1 page 1685, left-hand column, paragraphs 1,2 figure 3 ---	49, 53-56, 140
A	SUMMERFIELD A ET AL: "Lymphocyte apoptosis during classical swine fever: implication of activation-induced cell death." JOURNAL OF VIROLOGY, (1998 MAR) 72 (3) 1853-61. , XP002122828 page 1857, right-hand column, paragraph 2 -page 1858, left-hand column, paragraph 2 page 1858, right-hand column, paragraph 1 page 1859, right-hand column figure 8C ---	49, 53-56, 140
A	LEE J W ET AL: "HLA-DR-mediated signals for hematopoiesis and induction of apoptosis involve but are not limited to a nitric oxide pathway." BLOOD, (1997 JUL 1) 90 (1) 217-25. , XP002122829 abstract page 217, left-hand column, paragraph 2 -right-hand column, paragraph 1 ---	1-12, 18-20, 22-28, 39-46, 79-83
A	GENESTIER L ET AL: "Caspase-dependent ceramide production in Fas - and HLA class I-mediated peripheral T cell apoptosis." JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 FEB 27) 273 (9) 5060-6. , XP002122830 page 5060, left-hand column, paragraph 2 -right-hand column, paragraph 1 page 5061, left-hand column, paragraph 1 figure 7 ---	1-49, 52-56, 59-83, 138-142
A	SATOH T ET AL: "CHANGES IN MITOCHONDRIAL MEMBRANE POTENTIAL DURING OXIDATIVE STRESS-INDUCED APOPTOSIS IN PC12 CELLS" JOURNAL OF NEUROSCIENCE RESEARCH, US, WILEY-LISS, vol. 50, no. 3, page 413-420 XP002058714 ISSN: 0360-4012 abstract page 413, paragraph 2 -page 414, paragraph 2 ---	1-49, 52-56, 59-83, 138-142
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## INTERNATIONAL SEARCH REPORT

Inter. Application No  
PCT/US 99/06874

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 02579 A (UNIV EMORY) 22 January 1998 (1998-01-22) page 3, line 24 -page 5, line 9 page 13, line 17-20 ---	59-73
A	HERMESH O ET AL: "Mitochondria uncoupling by a long chain fatty acyl analogue." JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 FEB 13) 273 (7) 3937-42. , XP002122831 abstract -----	3,7,25, 46,52

# INTERNATIONAL SEARCH REPORT

Information on patent family members

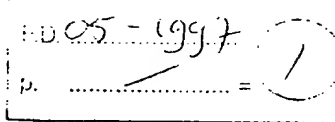
International Application No

PCT/US 99/06874

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9802579 A	22-01-1998	AU 3658797 A	09-02-1998
		CA 2260766 A	22-01-1998
		EP 0918882 A	02-06-1999
<hr/>			



XP-002122832



AN - 97302905 MEDLINE  
DN - 97302905

TI - Interferon-gamma enhances susceptibility of cervical cancer cells to lysis by tumor-specific cytotoxic T cells.

AU - Street D; Kaufmann A M; Vaughan A; Fisher S G; Hunter M; Schreckenberger C; Potkul R K; Gissmann L; Qiao L

CS - Department of Obstetrics and Gynecology, Stritch School of Medicine, Loyola University Medical Center, Maywood, Illinois 60153, USA.

SO - GYNECOLOGIC ONCOLOGY, (1997 May) 65 (2) 265-72.  
Journal code: FXC. ISSN: 0090-8258.

CY - United States

DT - Journal; Article; (JOURNAL ARTICLE)

LA - English

FS - Priority Journals; Cancer Journals

EM - 199708

EW - 19970802

AB - Recently we have demonstrated that tumor-specific cytotoxic T lymphocytes (CTLs) can be activated by cervical carcinoma cells expressing the costimulatory molecule CD80, which may be used as a therapeutic vaccine for patients with cervical cancer. For activated CTLs to be effective, appropriate amounts of MHC class I expression are required on target tumor cells. In this study, we found that some cervical carcinoma cells expressed only low levels of MHC class I and adhesion molecules such as CD54. We further demonstrated that tumor cells (CaSki and SiHa) expressing low levels of MHC class I were more resistant to lysis by specific CTLs than tumor cells (HeLa) expressing high levels of MHC class I. Treatment of CaSki or SiHa cells with interferon-gamma resulted in an increased expression of MHC class I, MHC class II, and CD54. Expression of CD58 and CD80 was not up-regulated or induced. Treatment of the tumor cells with interferon-gamma significantly enhanced the lysis of the tumor cells by specific CTLs which had been activated by the respective CD80-expressing tumor cells. The enhancement of cytolysis could be blocked by monoclonal antibodies to MHC class I and CD54, but not by that to MHC class II. Furthermore, we found that interferon-gamma induced apoptosis in cervical carcinoma cells but not in tumor-specific CTLs.